The present invention concerns new applications of pharmaceutical compositions, which contain crosslinked or uncrosslinked and preferably langkettige hyaluronic acid as well as conventional pharmaceutical auxiliary and/or inertial materials. An aspect concerns the use of a composition, the hyaluronic acid associated with heparin contains, to the delayed release of heparin, z. B. with the Wund, scar and Keloidbehandlung, to the inhibition of the blood coagulation or to the pain satisfying. An other aspect of the invention concerns the use of an hyaluronic acid of contained pharmaceutical composition to the treatment of viral infections, in particular to the treatment of an infection with herpes viruses. Still another other aspect of the invention concerns the use of an hyaluronic acid of contained pharmaceutical composition as analgesic, in particular to the application in range of nerve ends. Finally still another other aspect of the invention concerns the use of an hyaluronic acid of contained pharmaceutical composition for the rationalisation of skin, in particular for the durable reduction of wrinkles within the face range.

Hyaluronic acid is a not sulfated Glykosaminoglykan, which occurs in the human body in Synovialflüssigkeit as well as in extracellular Matrices. It becomes multiple used as building block for biocompatible and biological degradable polymers in various medical applications.

The European patent 0,619,737 concerns a pharmaceutical composition to the not topical Wund, scar and Keloidbehandlung, which contain or several crosslinked Glykosaminoglykane and conventional pharmaceutical auxiliary and/or inertial materials. As examples for Glykosaminoglykane become and. A. Hyaluronic acid and heparin mentioned. Further the combination of crosslinked Glykosaminoglykanen with other pharmaceutical agents, as for instance antibiotics, becomes disclosed.

Surprisingly now found became that a pharmaceutical composition, the crosslinked or uncrosslinked hyaluronic acid, preferably langkettige hyaluronic acid, associated with heparin, preferably with kurzkettigen heparin, a chain length of z. B. 5 to 10 Saccharideinheiten exhibits, to the delayed release of heparin, for example for local applications, as for instance to the Wund, scar and Keloidbehandlung, or to the pain satisfying, in addition, is for systemic applications, as for instance to the inhibition of the blood coagulation, suitable. The hyaluronic acid serves - beside its own favourable physiological effects - as matrix, in order to make a controlled release possible from heparin to. The rats of the release its association with the hyaluronic acid controlled can become over the degree of crosslinking and the type of the crosslinking of the hyaluronic acid as well as the type of the heparin and.

The composition according to invention affects inhibitive the Keloidbildung, in particular if it becomes non-topical (intraläsional) applied. By administration of the compositions according to invention scars of all type, leave themselves also deep scar formations in the connective tissue like z. B. the Dupuytren' disease of the palms or the so called Induratio penis plastica (IPP), which without preceeding injury (continuity separation) develop, successful treat.

The composition exhibits a number of advantages opposite known preparations. Like that a to a large extent pain-free administration is possible by injection. Also no local over reactions arise likewise no undesirable systemic side effects. An other advantage is the biological degradable in the organism. An advantage in relation to the,619,737 compositions disclosed in the European patent 0 consists in particular of it that the release rate of the heparin can become varied depending upon application, z. B. after type of the used Hyaluronsäurematrix and the used heparin. So an essentially constant release rate of the active ingredient can both with local and with systemic applications for a longer period, z. B. 1 week or more, achieved becomes.

Furthermore the composition is suitable also for other known pharmaceutical applications of the heparin both for systemic and local applications, z. B. to the inhibition of the blood coagulation. In addition the composition can become also in form of an implant by surgical procedures applied.

A subcutaneous administration of the preparation at patients to the Thromboseprophylaxe could become to a large extent pain-free performed. The administration became multiple repeated in intervals of 7 days.

The hyaluronic acid knows z in more uncrosslinked or more crosslinked. B. covalent or non-covalent more crosslinked, form used become. The preparation of the crosslinked hyaluronic acid can take place actual on known manner. The covalent crosslinking made thereby generally by crosslinking with bifunctional reactive agents, like z. B. Glutaraldehyde or carbodiimide; over bifunctional amino acids, z. B. Lysine, protamines or albumins. Z can do. B. in addition, crosslinking over an amide bond prepared becomes. Other suitable reagents to the covalent crosslinking of hyaluronic acid are ethyl glycol or 1,4-Butandioldiglycidylether, Divinylsulfon, photo transverse cross-linking reagents, like Ethyleosin, hydrazides, like Bishydrazid, Trishydrazid and polyvalente Hydrazidverbindungen. Further intra and/or intermolecular esterified Hyaluronsäurederivate can become also used.

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Particularly prefered is a non-covalent crosslinking using multi-valued metal ions, as for instance irons, coppers, zinc, calcium, magnesium, barium and other chelatierenden metal ions.

Hyaluronic acid is in the crosslinked state commercial available and can then after association with heparin used according to invention become (z. B. Hylon TM and Hylagel TM, a crosslinked hyaluronic acid of the companies Bio matrix, NJ, the USA; to the preparation see. also US-A-4713448, US-A-4605691, APC TM of the companies Fidia, Inc. ore TM of the companies Anika Therapeutics or intergel TM of the companies Running core).

In a particularly prefered embodiment langkettige hyaluronic acid (molecular weight preferably between 10 4< becomes> to 10< 6> There, in particular between 10< 5> and 10< 6> There) used; the degree of crosslinking can remain small then. With higher degree of crosslinking also kurzkettige hyaluronic acid is suitable, whereby also molecules with small chain length of only few, z. B. >/= 10, preferably >/= 20 Saccharideinheiten, used to become to be able.

The association of the heparin with the hyaluronic acid can do covalent or non-covalent, z. B. via chemical crosslinking or via Chelatbildung, like explained above, take place. The Chelatbildung preferably physiological compatible multi-valued metal ions, as for instance mg 2+<,> become approx.< 2+>, Zn< 2+>, Fe< 2+> or Fe< 3+>, used.

The pharmaceutical compositions according to invention preferably contain the hyaluronic acid in amounts from 0,01 to 20 Gew. - %, related to the entire pharmaceutical composition, in particular in an amount from 0,01 to 5 Gew. - % and particularly prefered in an amount from 0,01 to 1 Gew. - %.

The portion of heparin in the compositions can become in other ranges varied and hangs of the size and type (z. B. crosslinked and uncrosslinked) of the heparin as well as its association with the hyaluronic acid and the intended type and duration of the application off. Generally the portion is within the range of 0,1 to 20 Gew. - %, related to the entire pharmaceutical composition, in particular from 0,5 to 10 Gew. - % and particularly prefered from 1 to 5 Gew. - %. The heparin can be present depending upon application in langkettiger or kurzkettiger, crosslinked or uncrosslinked form. Preferably kurzkettiges heparin with a size of 5-50, in particular 5-10, becomes Saccharideinheiten used.

The pharmaceutical compositions according to invention can be present in the form of by injection or surgical interventions applizierbaren preparing and in particular in form of injectable or implantable gels or solutions, preferably with a water content from 60 to 99 Gew. - %, or in addition, as anhydrous preliminary stage, z. B. lyophilized powders in form of a propellant. When pharmaceutical auxiliary and inertial material can do for this conventional, for which application according to invention suitable and with hyaluronic acid and heparin become compatible fabrics used. The prefered inertial material is water or an aqueous buffer solution.

As pharmaceutical adjuvants the pharmaceutical compositions according to invention, z can. B. Agents to the pH value adjustment, stabilizing agent, Antioxidantien, solubilizer, penetration-promoting agents, preservative and/or Gelbildner contain, as they become usually used in such compositions. They become used in in such preparing the conventional amounts.

The pharmaceutical compositions according to invention can if necessary contain beside the actual active ingredients hyaluronic acid plus heparin also still other pharmaceutical agents, which are compatible with the hyaluronic acid and the heparin in the frame of the application, of z. B. Active ingredients to the therapy of skin diseases (Dermatosen), antibiotics, z. B. Gentamycin, vancomycin, penicillins or cephalosporins, sulphonamides, disinfectant, hormones (z. B. Corticoide) and hormone descendants (z. B. Cortisol), local anaesthetics, z. B. of the type of the lidocaine or Novocains, vasoaktive substances to the Gefässkonstriktion (avoidance of bleedings), adrenalin, enzymes, like z. B. Hyaluronidase, interleukins, growth factors, z. B. EGF, PDGF and or IGF, skin care means and/or blood circulation-promoting (hyperämisierende) agents. The other active ingredients can be with the hyaluronic acid associated, z if necessary. B. by covalent or non covalent interactions.

With prefered a according to invention application in form of an injection the preparing, z can. B. to the avoidance of pains with the parting with the Injektionskanüle, local anaesthetics contain.

The preparation of the compositions according to invention can take place on a conventional, general known manner actual for the preparation of such compositions. The sequence of the mixture of the individual components is usually not critical.

The type, dose and frequency of administration of the composition according to invention as well as the nature (z. B. ) In particular z depend viscosity, degree of crosslinking, active substance content etc. after the type and severeness of the disease as well as on the general state of the patient and the state of the application place. B. the state and the sensitivity of a scar and the skin or a wound after a surgical intervention. If the compositions according to invention in form become topical applizierbarer preparing administered, then the administration usually corresponds for such compositions to the usual conditions.

The type of the treatment and the frequency of the application depend in particular also on individual responding of the persons which can be treated. A preferably made application of gels or solutions in distances from several days to 1 or 2 months, in particular approx. 1 to 2 weeks.

If the compositions according to invention in form of injectable gels become intraläsonal applied, then this is preferably done via injection with the help of fine cannulas and with pressure resistant syringes. In addition, the gels according to invention can be shot in by printing apparatuses transdermal; for this printing apparatuses can become used, as they are in the medicine for a such application known. Certain preparing can do also systemic, D. h. into the circuit or in body cavities, z. B. after surgical interventions, administered become. Implantable compositions preferably lie in the form of viscous gels and/or. Solutions, so called Instillationslösungen forwards.

Due to the association with langkettiger hyaluronic acid uncrosslinked and even kurzkettiges heparin can become as active ingredient by injection applied. - Without the association with hyaluronic acid - taking place the rapid evacuation of the heparin of the effect place becomes according to invention avoided by the compositions. The heparin remains dependent by the degradation that Hyaluronsäure matrix and by the kind of connection over days, weeks or months at the location of the application, z. B. in the Keloidgewebe, effective. Particularly prefered is the duration of effect of 5-20 days, z. B. approx. 1-2 weeks.

An advantage of the prefered preparing according to invention, z. B. in form of injectable or implantable gels and their

application, exists also in the fact that after healing the injection sites and/or. the surgical seams no hygienic additional measures required are. All body regions equally treated can become, and the mobility of the patients is not limited by dressings. By the treatment with the preparing according to invention an occurrence or a recurrence of Keloiden can become prevented, which shows its preventive effect.

An other embodiment for the prevention of Keloiden or contracts scars is the application of anhydrous compositions (z. B. as Lyophilisat) in form of a Wundpuders in fresh wounds or body cavities. The propellant becomes scattered thereby before the Wundverschluss in the open wound or Wundhöhle. Then the made Wundverschluss by seam, by parentheses o. A. The propellant takes up waters from the tissue in the wound and corresponds then to the preparation according to invention in form of a gel and/or. even a preparation according to invention represents.

Compositions in propellant or gel form can become the prevention of undesirable growing together also in large body cavities introduced, z. B. in the belly or chest cavity, during a surgical intervention at the intestine or at the lung, into the heart bag, or after surgical interventions over located drainages. With inflammatory Ergüssen in large body cavities the preparation according to invention can become also after Punktion and emptying of the Ergusses over the located cannula introduced.

Also in from the outside accessible cavities and aisles of the body the preparation according to invention introduced can become, z. B. in the nose main and - beside-hollow and/or. Nose courses or into the tear channels to the prevention of scarred growing together, eventual also on a suitable carrier (z. B. Tampon).

Still another other aspect of the invention are new applications of pharmaceutical compositions, which contain crosslinked or uncrosslinked hyaluronic acid as active ingredient. With these compositions regarding its content to hyaluronic acid as well as its application forms to the embodiments one refers above.

In a first aspect these compositions become the treatment of viral infections provided, for example with the treatment of infections with the neuro tropics viruses, as for instance herpes viruses, z. B. Herpes simplex or herpes more zoster. The application can take place depending upon type of the viral infection local or systemic. Preferably the composition becomes the treatment of dermal or mucosalen Herpesinfektionen, z. B. Herpes labialis or herpeses genitalis, used. Other prefered applications are the treatment of infections with hepatotropen viruses, as for instance hepatitis viruses, z. B. Hepatitis A, B, C viruses, the treatment of infections with immunotropen viruses, z. B. HEAVE, cytomegalovirus, or the treatment of infections with other neuro tropics viruses, z. B. Polio. Further also infections with other viruses treated can become, the diseases of the eyes, z. B. Keratoconjunctivitis epidemica, or the respiratory tracts, z. B. Colds, cold or flu, cause. Examples of such viruses are Rhino and influenza viruses. In some cases a local is, z. B. topical or transdermal application prefered. Other prefered application forms are ophthalmic compositions or compositions for nasal administrations, z. B. Drop, spray and inhalierbare aerosols. On the other hand the composition can do also systemic, z. B. by intravenous injection or oral as drinking or rinse solution, z. B. the fight against infections of the stomach and intestinal tract or the throat, administered become. Particularly prefered is in or multiple prophylactic administration before onset of an acute disease.

Surprisingly with administration of the composition in form of a gel through intra or subdermale injection was found into the affected area with patients with rezidivierenden herpeses labialis that the onset of the infection could become at least to a large extent prevented. After administration of the compositions the patients were free of Efloreszenzen. Particularly effective was the administration in the Prodromalstadium with occurrence of itching. If necessary the administration of the composition prophylactic in larger time intervals, z can. B. from 3 months, repeated become.

An other application of the hyaluronic acid contained compositions is the use as analgesic, preferably as peripheral acting analgesic, in particular to the application within the range of nerve ends, z. B. of injured nerve ends for example after cuts. The application can thereby as described, for example local via injection to take place before. The administration of the composition in operative wounds, z. B. as propellants, gel or solution before Wundverschluss, guided in several cases to a significant Schmerzlinderung and also to a significant reduction of the need at additional peripheral and/or. central pain means.

Still another other application of the hyaluronic acid contained compositions is the rationalisation of skin. Surprisingly found became that with application of the compositions a durable, D. h. over a period of at least 6 months and in particular over effect achieved recognizable to several years will can. Like that the front folds were visible reduced with several patient an year after application of the composition. The compositions are thus suitable as “elevator serum” for the rationalisation of face skin and can contribute to avoid surgical interventions to face rationalisation. The application is preferably transdermal, z. B. via injection or with one of the before described transdermal application systems, and can take place punctually and/or planarly at the skin portions which can be tightened.

Hyaluronic acid can become also infiltration solutions added, which become injected before a fat exhaust (Liposuction) first into the tissue. Such infiltration solutions are usually isotonic or hypotonic saline solutions, which can contain additions, and/or pain-reducing additions for example container-contracting, as for instance Noradrenalin, adrenalin, lidocaine, Prilocain, bicarbonate, corticosteroids etc. These solutions becomes hyaluronic acid (crosslinked and/or not-crosslinked hyaluronic acid) in concentrations of favorable-proves 0.001 to 1.0% (thread/volume.), preferably 0.01 to 0.5% (thread/volume.), z. B. about 0.025% (thread/volume.) added. It was found that becomes mechanical facilitated by the Hyaluronsäurezusatz the procedure of the fat exhaust, D. h. the handling the suctioncure-saved, which becomes moved by the fatty tissue, requires less energy expenditure. Further obtained-worth structures of the fatty tissue become, like z. B. Blood vessels, nerves or Bindegewebsbänder, preservation. The procedure of the fat exhaust becomes more atraumatisch by the Hyaluronsäurezusatz, in the comparison the conventional procedure, also significant. Finally the flow properties of the Fettgewebeaspirates improve by the Hyaluronsäurezusatz for infiltration solution, so that with smaller vacuum can be worked. Also this leads to a reduction of fabric trauma. Altogether the effected addition from hyaluronic acid to the infiltration solution a indulgence of the remaining fatty tissue in the organism as well as a more careful removal of the Fettgewebeaspirats. Thus the survival is improved by fat cells in the Aspirat.

This is to that extent of importance, since Fettgewebsaspirate as body-own grafts used to become to be able. The fat cells are preserved by addition from hyaluronic acid to the infiltration solution with removal, so that becomes observed in case

of the transplantation increased increasing of the transfered tissue at the receiver place. Thus hyaluronic acid becomes particularly prefered the infiltration solution added whenever the sucked off fatty tissue is to become transfered as autologes graft to other sites of the body. A subject-matter of the invention is thus a Fettgewebsaspirat, which hyaluronic acid (crosslinked or not-crosslinked) contains.

Particularly prefered becomes the Fettaspirat for cosmetic purposes, z. B. to the Aufpolsterung of soft parts in the face, used. Here the Aspirat becomes by thin cannulas with for example 1-2 mm diameter into the receiver place used. The presence of hyaluronic acid in the Aspirat and/or. Graft leads to an ease of the passage of the tissue by the cannula. This means a smaller pressure application to the transport by the cannula, a smaller Traumatisierung of the transfered tissue and/or a higher increasing rate of the transfered tissue at the receiver place.

Hyaluronic acid according to invention the contained Fettgewebeaspirat can also after conventional suction (without addition of hyaluronic acid) in higher concentration, z. B. 0.1-1% (thread/volume.) the Fettgewebsanteil (fraction) of the Aspirats added which can be transferred become, which likewise leads to an increased Einheitlungsrate of the transfered tissue.

General one knows a Hyaluronsäurezusatz (crosslinked and/or not-crosslinked) z. B. with the transmission of grafts of autologer or xenogener tissues and/or more autologer or more xenogener more loosely and/or. separated cells, which are not united in a fabric federation, by kanülenförmige applicators the survival and/or increasing the transfered fabric particles or cells improve.

It is already known that cells, which are late provided for a transmission into a receiver organism in a culture with hyaluronic acid become treated. It was however found that the concentration of the hyaluronic acid is not in such cultures sufficient, in order to ensure with the transmission by thin cannulas a protektiven effect. It is advisable to accomplish before the transmission of such cells still another Hyaluronsäurezusatz according to invention whereby a final concentration from 0,05 to 1.0% favorable-proves, in particular from 0,1 to 0.5% (thread/volume.) hyaluronic acid adjusted becomes.

So far a transmission of fabric particles and/or. - cells in body cavities made, works hyaluronic acid additional becomes as lubricant and concomitantly as protective film for grafts, z. B. in the heart bag, in the Pleuraspalt or in the peritoneum, there in these cavities and/or. Spalträumen of organs against each other shifted become. Hyaluronic acid is to be finally used thereby also as lubricants in the aforementioned Spalträumen.